Searching for the Optimal Resuscitation Method: Recommendations for the Initial Fluid Resuscitation of Combat Casualties

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Resuscitation can exacerbate cellular injury caused by hemorrhagic shock, and the type of fluid used for resuscitation may play an important role in this injury. Unlike some factors in the treatment of combat casualty, the method of resuscitation is under our control. The prevention of cellular injury through wiser resuscitation strategies would be more advantageous than attempting complex immunomodulation after the damage has already occurred. This article summarizes data from a number of studies to illustrate the differential effects of commonly used resuscitation fluids on cellular injury. Our findings show that resuscitation with hypotonic/isotonic crystalloids, including lactated Ringer's (LR) solution, and artificial colloid solutions, elicit severe immune activation and an up-regulation of cellular injury markers. This effect is not seen with plasma, natural colloids (albumin), and fresh whole blood. Hypertonic fluids cause suppression of neutrophil activation and a milder increase in the expression of cell injury markers compared with isotonic fluids. The effect of various resuscitation fluids on core cellular functions such as gene regulation is also summarized in this article. Finally, because of the uniqueness of combat care, a set of new recommendations for initial fluid resuscitation of combat casualties is proposed.

Key Words: **Combat casualty, Military, Fluids, Resuscitation, Hemorrhage, Cellular injury, Neutrophils, Adhesion molecules, Apoptosis, Ketone bodies, Hypertonic saline, Gene regulation, Recommendations.**

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The single major cause of death in potentially salvageable battlefield casualties is hemorrhage.[1] Approximately 20% of these deaths are preventable if the bleeding can be quickly controlled or minimized.[2,3] In addition to controlling hemorrhage, the combat casualty is often treated with resuscitation fluids. There have been no significant changes in the methodology of fluid resuscitation since the Vietnam War era. These resuscitation protocols are adopted mostly from civilian trauma literature despite recent data proposing methods especially designed for the treatment of traumatic hemorrhage in the battlefield.[4] At present, there is no clear consensus regarding the optimal resuscitation strategy for combat casualties.

It is now being recognized that resuscitation fluids are not completely innocuous, and that they may actually potentiate the cellular injury caused by hemorrhagic shock.[5] This concept of "resuscitation injury" has steadily gained attention since the Vietnam conflict. It was during this period that the appearance of "shock lung/Da Nang lung" (later termed acute respiratory distress syndrome) was first described in soldiers that received massive crystalloid resuscitation. Today, acute respiratory distress syndrome and multiple organ dysfunction syndrome are major causes of delayed mortality in trauma patients.[6] This raises a very important question: Is the resuscitation injury purely a reperfusion phenomenon or does the type of fluid infused altar the degree of subsequent cellular damage? Tissue beds during shock have "low flow" but they rarely reach a state of "no flow." Thus, the classic paradigm of ischemia-reperfusion may not explain all the facets of cellular injury under these conditions. It is entirely possible that the type of fluid that we use for resuscitation contributes to this injury. It is generally accepted that the cellular damage sustained during resuscitation is multifactorial in cause. Its intensity depends on the severity and duration of hemorrhagic shock, presence of associated injuries and comorbid diseases, second-hit insult, and our resuscitation approach, to name just a few. However, as compared with most of the other variables, the resuscitative strategy is entirely under our control. We choose the nature of the fluids, their rate of administration, and the endpoints of resuscitation. We also may decide not to resuscitate in selected patients. All these issues assume even more importance in the setting of limited resources and

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long delays to definitive care, as expected in the combat zones of the future.

The Trauma Research and Readiness Institute for Surgery at the Uniformed Services University of the Health Sciences has been involved in studying the differential effects of various resuscitation fluids on cellular responses. Listed below are the summaries of some of the experiments. Although cellular injury during the postresuscitation period involves almost all organs through multiple interconnected cascades, for ease of presentation our findings will be discussed under three broad categories: (1) effect on neutrophils (data from animal models of hemorrhagic shock and in vivo testing of human blood are discussed); (2) effect on tissues and organs (this section summarizes the impact of resuscitation fluids on various markers of cellular injury including alterations at the level of gene regulation); and (3) development and testing of novel resuscitation fluids. Finally, we recommend an algorithm for the initial resuscitation of combat casualties.

NEUTROPHIL FUNCTION

Aberrant activation of neutrophils and altered interactions between neutrophils and endothelial cells play a critical role in the postresuscitation organ injury.[7–9] Our laboratory has tested the effects of various resuscitation fluids on neutrophil function using both in vivo and in vitro models.

Animal Models of Hemorrhagic Shock

In a swine model of volume-controlled (40% total blood volume) hemorrhagic shock using unanesthetized animals, resuscitation with lactated Ringer's (LR) resulted in an increased neutrophil activation.[10] Activation was defined as increased neutrophil oxidative burst activity, which was measured in a whole blood assay using flow cytometry. We found no neutrophil activation during the hemorrhage or shock period (60 minutes). However, significant increase in neutrophil oxidative burst activity was noted after the resuscitation phase. This observation was not surprising, as it is supported by the traditional concept that reperfusion of ischemic tissues sets into motion numerous cascades of adverse events. The unexpected result that challenged this simple explanation was the fact that infusion of LR without hemorrhage also caused neutrophil activation (Fig. 1). Furthermore, neutrophil activation was not observed after resuscitation with fresh whole blood or 7.5% hypertonic solution (HTS). Taken together, these findings suggested that it is not merely restoration of flow that is important, but that an equally critical variable is the type of fluid used to achieve this goal.

With this information, the next study examined whether the observed effects of LR on neutrophil activation were dose and rate dependent. Again, a swine model of volume-controlled hemorrhagic shock was used. Animals were resuscitated with three times the volume of LR either over 1 hour (high-volume, fast-rate group) or 3 hours (high-volume, slow-rate group). Another group was resuscitated over 1 hour with a volume of LR equal to lost blood (low-volume, slow-rate group). The highest degree of neutrophil activation was seen in the high-volume, high-rate group, followed by the low-volume, slow-rate and high-volume, slow-rate groups, respectively (Fig. 2). However, all three LR infusion protocols were associated with significantly increased neutrophil activation compared with anesthesia alone or hemorrhage and sham resuscitation.[11] Resuscitation with Dextran and Hespan (artificial colloids) was even more stimulating than LR (Fig. 3). Fresh whole blood and natural colloid (5% albumin and 25% albumin) resuscitation did not cause neutrophil activation in this experiment.[12]

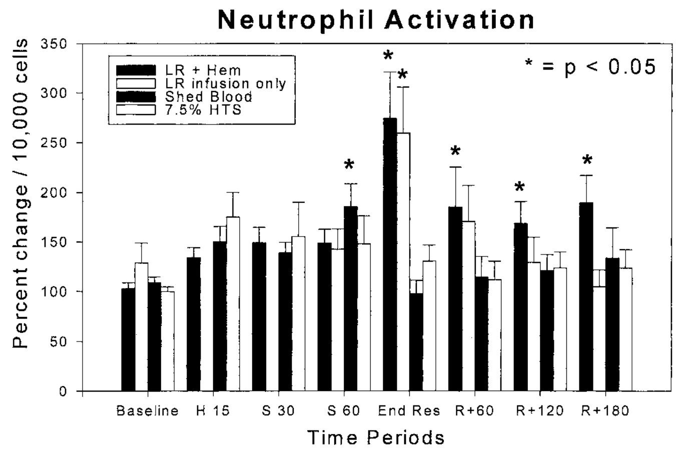

Fig. 1. *Neutrophil oxidative burst activity. Neutrophil fluorescence (measured by flow cytometry) reported as percentage change from baseline values per 10,000 cells ± SEM.* *p < 0.05*, compared with baseline values, analysis of variance with Tukey's* b *multiple comparison test. Baseline, before hemorrhage; H 15, end of 15-minute hemorrhage (28 mL/kg); S 30, 30 minutes into shock period; S 60, 60 minutes into shock period; End Res, end of 60-minute resuscitation period; R + 60, 60 minutes after end of resuscitation; R + 120, 120 minutes after end of resuscitation; R + 180, 180 minutes after end of resuscitation; LR + Hem, hemorrhagic shock and LR resuscitation; Shed blood, hemorrhagic shock and shed blood resuscitation; 7.5% HTS, hemorrhagic shock and 7.5% hypertonic saline resuscitation.*

Human Neutrophil Studies

Findings from our animal models were substantiated by testing the effect of various resuscitation fluids on human neutrophils using blood from healthy volunteers. A whole blood assay was used to avoid neutrophil activation during the isolation process. Our findings revealed that exposure of human neutrophils to isotonic crystalloids and artificial colloids caused a significant increase in the oxidative burst activity in a dose-dependent fashion, whereas albumin (5% and 25%) and hypertonic saline did not activate the neutrophils (Fig. 4*A*). Using the same method, we also studied the expression of neutrophil adhesion molecule (CD18). Artificial colloids (dextran and Hespan) caused the highest expres-

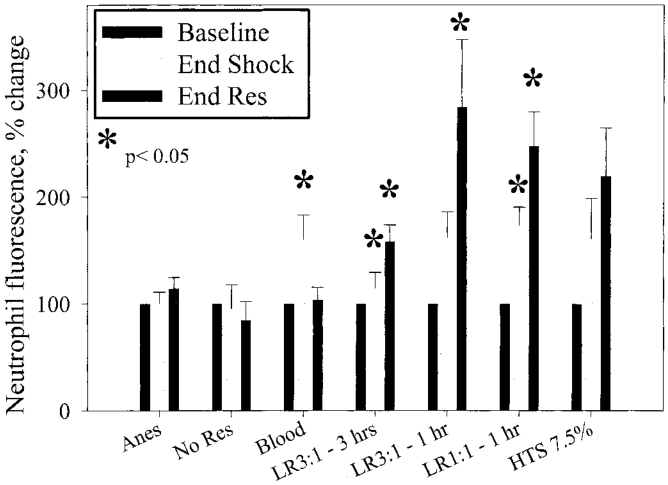

Fig. 2. *Neutrophil oxidative burst activity. Neutrophil fluorescence measured by flow cytometry and reported as percentage change from baseline values ± SEM.* *p < 0.05, *using* t *test compared with baseline values. Baseline, before hemorrhage; End Shock, end of 60-minute shock period; End Res, end of resuscitation period; Anes, anesthesia and sham hemorrhage; No Res, hemorrhage and sham resuscitation; Blood, hemorrhage and resuscitation with shed blood; LR3:1–3 hrs, hemorrhagic shock and 3:1 volume lactated Ringer's resuscitation over 3 hours; LR3:1–1 hr, hemorrhagic shock and 3:1 volume lactated Ringer's resuscitation over 1 hour; LR1: 1–1 hr, hemorrhagic shock and 1:1 volume lactated Ringer's resuscitation over 1 hour; HTS 7.5%, hemorrhagic shock and 0.3:1 volume 7.5% hypertonic saline resuscitation over 1 hour.*

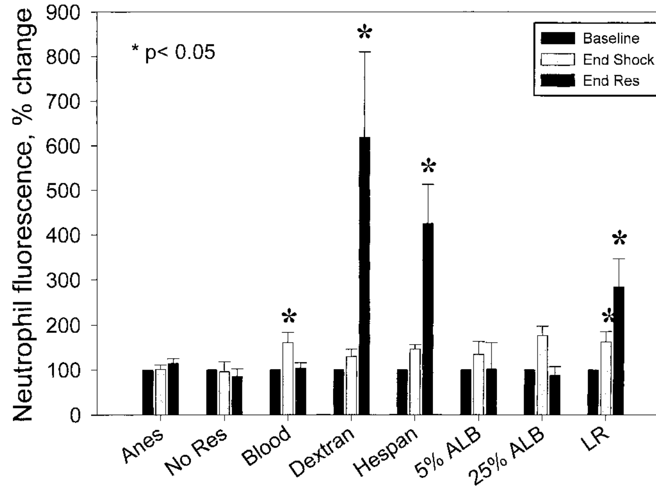

Fig. 3. *Neutrophil oxidative burst activity. Neutrophil fluorescence measured by flow cytometry and reported as percentage change from baseline values ± SEM.* *p < 0.05, *using* t *test compared with baseline values. Baseline, before hemorrhage; End Shock, end of 60-minute shock period; End Res, end of resuscitation period; Anes, anesthesia and sham hemorrhage; No Res, hemorrhage and sham resuscitation; Blood, hemorrhage and shed blood resuscitation; Dextra, shock and 1:1 volume dextran 40 resuscitation; Hespan, shock and 1:1 volume 6% hetastarch resuscitation; 5% Alb, shock and 1:1 volume 5% human albumin resuscitation; 25% Alb, shock and 0.2:1 volume 25% albumin resuscitation; LR, shock and 3:1 volume lactated Ringer's resuscitation.*

sion of CD18 (Fig. 4*B*). Once again, natural colloids (albumin) and hypertonic fluids did not cause any increase in CD18 expression.[13]

This study demonstrated that it was not the differences in electrolyte composition, pH, or osmolarity that accounted for the changes found in neutrophil activation. However, previous reports have shown that D-lactate, an isomer not naturally found in the human body, could have detrimental effects. Currently, solutions of LR that are commercially available contain equal amounts of both isomers: L-lactate and D-lactate (14 mmol/L). Again, studying human neutrophils in whole blood, we found that LR containing L-lactate (containing 28 mmol/L of L-isomer only) caused significantly less neutrophil activation compared with standard racemic LR. A similar attenuation of neutrophil oxidative burst was also seen when the D-L-lactate in LR solution was completely removed and replaced with ketone bodies (beta hydroxybutyrate).[14]

A combination solution of dextran and 7.5% saline is now being used in Europe for volume expansion. As dextran stimulates and hypertonic saline suppresses neutrophil oxidative burst activity, we were interested in evaluating the effect of this combination solution on neutrophil function. This was done, again using flow cytometric analysis of human blood, and our findings demonstrated that the hypertonic saline component of the solution exerts the dominant suppressive effect. The combination solution decreased neutrophil oxidative burst activity similar to hypertonic saline alone, and this effect was even more pronounced when the neutrophils were additionally stimulated with fMLP or *Escherichia coli*.[15]

MARKERS OF CELLULAR INJURY IN VARIOUS ORGANS

Expression of Adhesion Molecules

Once activated, neutrophils bind to the endothelial cells, establish firm adhesions, and finally migrate into the surrounding tissues (Fig. 5). This process involves numerous adhesion molecules. For example, the early rolling phase depends on the selectin group (L-, P-, and E-selectin), whereas the firm adhesion phase involves the beta$_2$ integrins (CD11/18) and their ligands: vascular cell adhesion molecule-1 and intracellular adhesion molecule-1. To determine whether the activation of circulating neutrophils was also associated with alteration in other aspects of the inflammatory process, we studied the expression of adhesion molecules in a rat model of hemorrhagic shock. The findings again demonstrated significant differences between commonly used fluids. LR resuscitation and even LR infusion (without prior hemorrhage) caused increased expression of these adhesion molecules in the lung and spleen. This increased expression was not seen in the nonresuscitated animals or in the animals

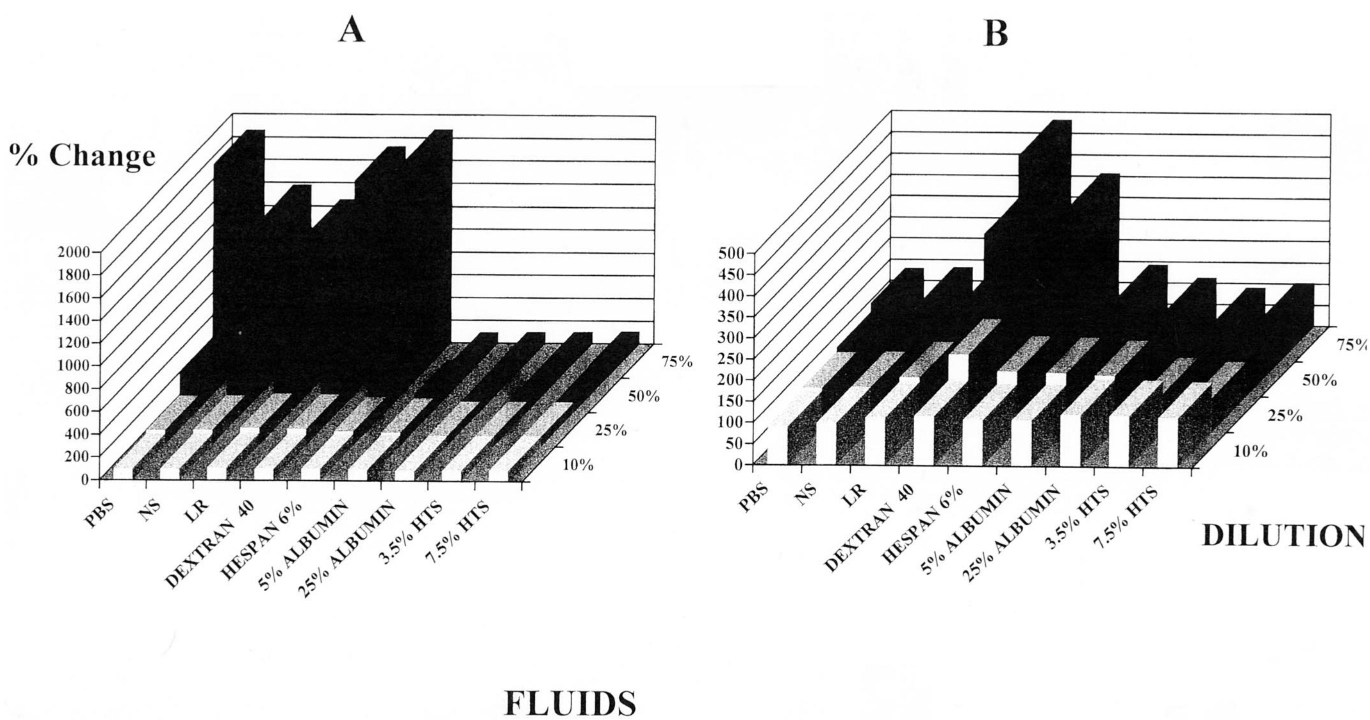

Fig. 4. *(A) Human neutrophil oxidative burst. Intracellular fluorescence after 30 minutes' incubation with various fluids at 10%, 25%, 50%, and 75% dilutions. (B) Human neutrophil CD18 expression. Immunofluorescence after 30 minutes' incubation with various resuscitation fluids at 10%, 25%, 50%, and 75% dilutions. Data presented as percentage change in fluorescence compared with normal saline at 10% dilution. PBS, phosphate-buffered saline; NS, 0.9% saline; LR, lactated Ringer's; HTS, hypertonic saline.*

resuscitated with fresh blood. When LR infusion was preceded by hemorrhagic shock, the increased expression of adhesion molecules was accompanied by histologic evidence of pulmonary edema and inflammation. The effect of hypertonic saline on adhesion molecules was better than LR but not as good as fresh whole blood.[16,17]

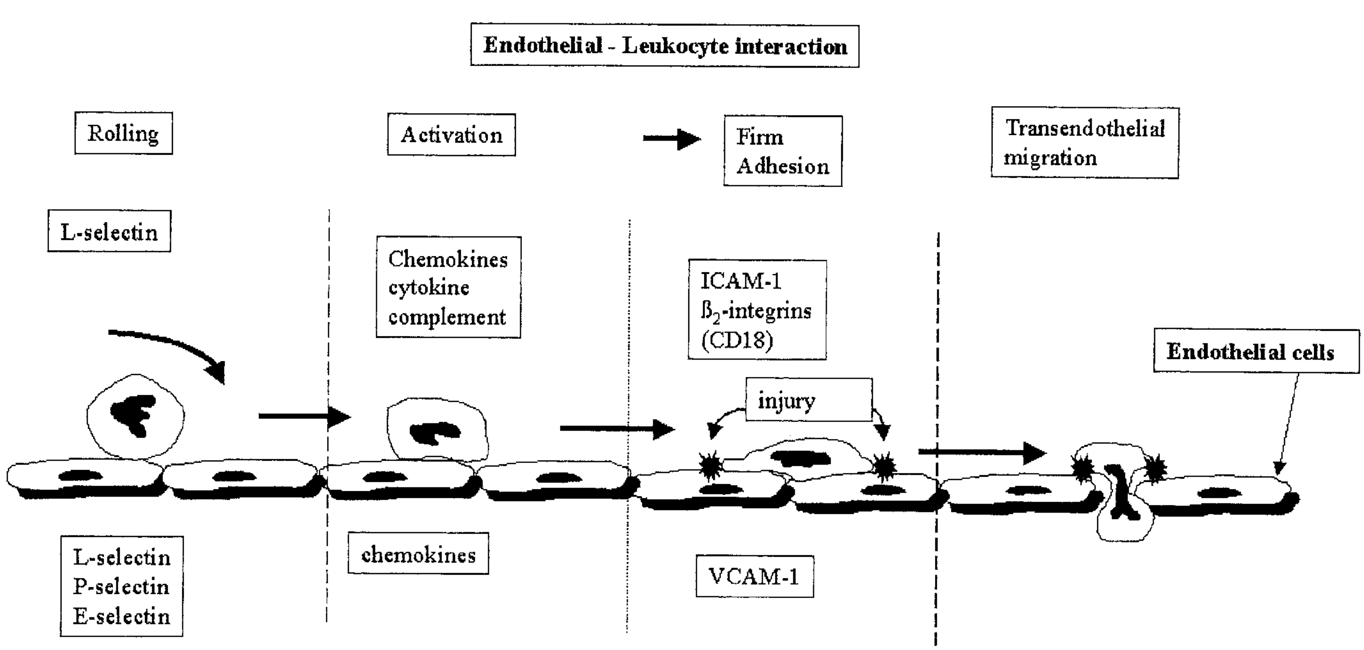

Fig. 5. *Various stages of neutrophil and leukocyte interaction. ICAM-1, intracellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1.*

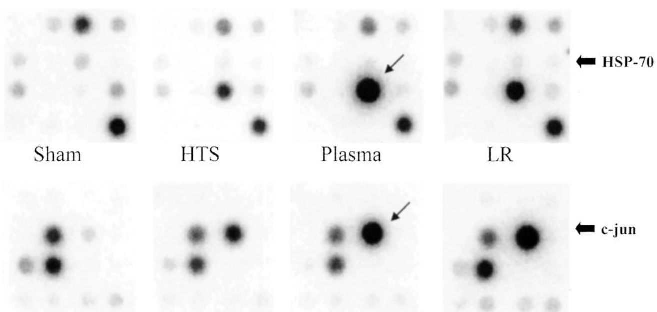

Fig. 6. *Sections of cDNA array showing differential expression of* HSP-70 *(above) and* c-jun *(below) in different experimental groups. Sham, sham hemorrhage; HTS, hemorrhage and 7.5% hypertonic saline resuscitation; Plasma, hemorrhage and plasma resuscitation; LR, hemorrhage and lactated Ringer's resuscitation.* Arrows *point to the genes of interest on the cDNA array.*

Cellular Apoptosis

Apoptosis is a highly specialized and well-regulated physiologic process for elimination of cells that represent a threat to the integrity of the organism. As apoptosis is a homeostatic mechanism for the removal of damaged cells, we used increased apoptotic cell death in various organs as a marker of cellular injury. In a rat model of hemorrhagic shock, it was demonstrated that LR resuscitation causes increased apoptosis in intestinal mucosa, smooth muscle, liver cells,[18] and lung.[19] In contrast, sham resuscitation, and resuscitation with plasma, fresh blood, and hypertonic saline did not induce significant apoptosis.

cDNA Array Analysis

With the recent availability of high-density cDNA array technology, we now have the capability to rapidly perform systematic, global evaluation of cellular functions and regulations at the genomic level. We therefore studied the acute impact of hemorrhagic shock and resuscitation on gene expression in major organs after application of different resuscitation strategies in rats. Expression of 1,176 genes in four different organs (spleen, lung, liver, and muscle) was determined after resuscitation with LR, plasma, and 7.5% HTS and compared with control group (sham hemorrhage). After resuscitation, 82 of the genes studied (7%) displayed an altered expression of at least twofold compared with the sham hemorrhage group. In these 82 genes, a total of 167 alterations (114 increased and 53 decreased expression) were noted. The largest number of altered expressions were noted in liver (63 of 167), followed by lung (n = 57), muscle (n = 25), and spleen (n = 22). The largest number of alterations was caused by plasma resuscitation (68 of 167), followed by LR (n = 51) and HTS (n = 48). For every organ studied, alterations in genetic expression were dependent on the fluid used for resuscitation.[20] Figure 6 shows differential expression of two such genes, *c-jun* and *HSP-70*, in the control and resuscitation groups.

DEVELOPMENT AND TESTING OF POTENTIAL RESUSCITATION FLUIDS AND METHODS.

In 1999, the United States Navy, through the Office of Naval Research, requested the Institute of Medicine (IOM) to examine the information available on resuscitation fluids. As a result of this process, the distinguished committee gathered by the IOM made a number of recommendations.[5] One of the recommendations was to modify the existing lactated Ringer's solution by eliminating D-lactate, reducing total L-lactate, and adding ketone bodies as an energy source. Following these recommendations, we have formulated and produced a product that we call "ketone Ringer's solution."

During hemorrhagic shock, administration of exogenous ketone bodies has clearly been shown to improve the metabolic profile[21] and inhibit protein catabolism[22] in animal models. Similarly, in severely injured patients, resuscitation with a ketone body (beta hydroxybutyrate) containing solution for the first 3 hours significantly decreases posttraumatic protein catabolism.[23] Beta hydroxybutyrate is also a membrane stabilizer and free radical scavenger. When tested in a severe model of hemorrhagic shock, ketone Ringer's solution significantly attenuated pulmonary apoptosis and decreased the expression of adhesion molecule (intercellular adhesion molecule-1) in rats (Fig. 7).[24] As seen in our previous models, plasma resuscitation did not cause any significant increase in cellular apoptosis. It was not clear whether it was the elimination of lactate or addition of ketone bodies that conferred these beneficial effects. Also, the efficacy of other energy substrates (such as pyruvate) in the setting of hemorrhagic shock warrants further testing.

In all of our experiments, we have included hypertonic saline as a potential resuscitation fluid. The rational for testing hypertonic saline in our experiments was because of the logistical advantage (weight and cube) it offers to a soldier who is already burdened with heavy gear. Our findings, similar to other studies in the literature, showed that HTS resuscitation in general suppressed inflammation and provided vascular volume restoration equal to other fluids. Other researchers have previously reported similar findings, but the subtle difference has been in the interpretation of the results. It has been assumed that cellular injury and immune activation seen with standard crystalloid resuscitation were an expected consequence of the preceding shock period. Almost all of the studies have used crystalloid resuscitation as the control group ("gold standard") to which other resuscitation strategies were compared. Our data emphasize an often overlooked fact, that although crystalloids may be the "standard of care," they are certainly not free of side effects. Hence, the observed cellular damage may not be purely because of "reperfusion" of ischemic tissues but the manifestation of a much more complex "resuscitation injury."

As a result of the favorable data in the literature, one of the final recommendations made by the 1999 IOM committee was to use hypertonic saline as the initial fluid for resuscita-

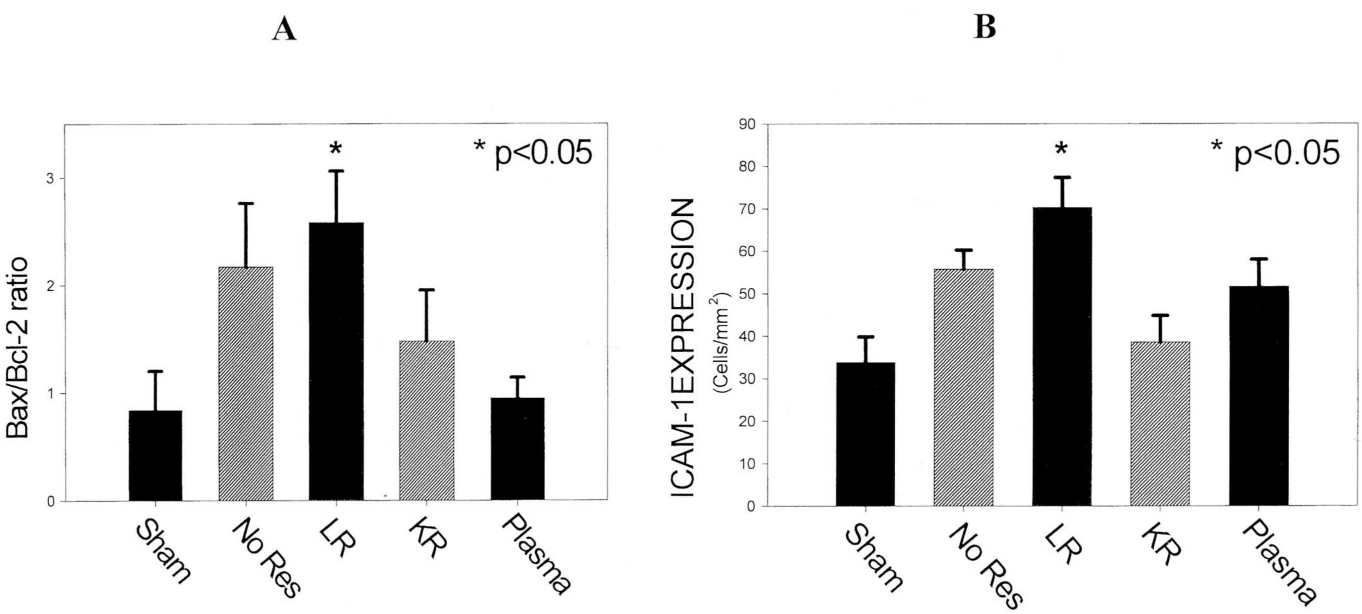

Fig. 7. *(A) Pulmonary apoptosis. Ratio of bax (proapoptotic) and bcl-2 (antiapoptotic) proteins in lung tissue of different groups as measured by Western blot analysis. (B) Intracellular adhesion molecule-1 expression as measured by immunostaining. Data presented as positive cells per millimeter squared at 40× magnification. All data shown as group means ± SEM. *p < 0.05, analysis of variance and Dunnett's test for multiple comparisons. Sham, sham hemorrhage; No Res, hemorrhage and sham resuscitation; LR, hemorrhage and lactated Ringer's resuscitation; KR, hemorrhage and ketone Ringer's resuscitation; Plasma, hemorrhage and plasma resuscitation.*

tion of combat casualty.[5] The report states: "The initial fluid resuscitation of the hemorrhaging battle field casualty should be a 250 mL bolus of 7.5% saline delivered by a rapid infusion system." Obtaining reliable intravenous access on the battlefield can be difficult; therefore, the committee proposed that the fluid could be infused through an intraosseous (IO) needle placed in the anterior tibia and the total volume of infusion should be kept under 500 mL. There were two concerning factors in this recommendation that we felt deserved further investigation. First was that in the setting of uncontrolled hemorrhage, would the bolus of 250 mL of 7.5% HTS (which is roughly equivalent to 2 L of 0.9% normal saline) cause more bleeding in contrast to smaller, more frequent volumes of infusion. The second concern was the method of infusion. Anterior tibial IO infusion had not been adequately tested in a dehydrated, long-term, survival model of hemorrhagic shock. To resolve these questions, 14 dehydrated Yorkshire swine had placement of a 12-guage needle in the right anterior tibia under isoflurane anesthesia. Uncontrolled hemorrhage was induced via left iliac artery and vein injury. Animals were kept in shock for 2 hours and then resuscitated over 2 hours with 5 mL/kg of 7.5% HTS given either as 10 small boluses (group I) or two large boluses (group II) to compare the physiologic response and blood loss. The control animals (group III) received an equal volume of 0.9% saline by IO infusion and additional saline intravenously to equalize the salt load in all groups. Our results showed HTS resuscitation was effective in dehydrated animals and did not increase the bleeding from the uncontrolled vascular injury. However, IO infusion of HTS in this model carried a very high rate of local soft tissue complications. Between the second and fifth postresuscitation days, the 7.5% HTS-resuscitated animals developed soft tissue necrosis (as a result of compartment syndrome) or bone marrow necrosis of the right hind leg (group I, 100%; group II, 66.6%; group III, 0%). We feel that, until further investigations are complete, the use of 7.5% HTS in humans should be limited to intravenous administration.[25]

Although hypertonic saline provides both the logistical advantage and possible immunosuppressive effects to help counterbalance the postresuscitation inflammatory response, it is still not the ideal fluid. This has led us to investigate other fluids including the possibility of using freeze-dried plasma. The concept of freeze-drying blood products is certainly not new. We have known for quite some time that plasma can be easily freeze-dried without damaging its proteins. For example, clotting factors are well preserved and remain functional even after 10 years of storage in a freeze-dried stage.[26] However, with the increasing popularity of crystalloid fluids, this option did not receive much attention. Now that we have the capacity to study the impact of fluids on cellular and subcellular functions, the beneficial properties of plasma are hard to ignore. The transport and storage of fresh frozen plasma in combat situations is logistically cumbersome, thus encouraging us to evaluate the use of freeze-dried plasma as an alternative. This product has a very long shelf life and can theoretically be made in advance for soldiers using their own plasma, thus eliminating the need for cross-match at the time of infusion. The powder can also be reconstituted quickly and dissolved in a small volume of solvent that would yield a hyperoncotic/hypernatremic fluid. The hemodynamic response to an infusion of this small volume of fluid is equal to the much larger volumes of isotonic crystalloids that are currently in use. We have also noted on a consistent basis that natural products (such as whole blood or plasma) had the most favorable effects on the cells and they did not cause immune overactivation. Although this seems intuitive, historically our goal has primarily been the restoration of hemodynamic parameters. The makeup of the solution was of no particular importance to the clinicians provided the desired hemodynamic results were achieved. For example, during the Korean War, blood and plasma were used for resuscitation, resulting in numerous saved lives, but during the Vietnam conflict, the use of blood products fell out of favor and the less expensive and easier to use crystalloids gained popularity. However, fresh plasma has many beneficial properties in addition to its ability to restore blood volume. If the freeze-dried plasma also exhibits these qualities, it may be of benefit in the setting of combat casualties.

CONCLUSION

An ideal fluid for the resuscitation of combat casualties (and civilian trauma victims) should be safe, efficacious, cheap, and easy to store and transport (especially important for the military); should have the capacity to carry oxygen and nutrients to the cells; and should protect the cells from resuscitation injury. Unfortunately, such a fluid is not available today. Because of the emerging data on fluid cytotoxicity, we should consider resuscitation fluids as drugs, with well-defined indications and contraindication for use, safe dosages, and side effects. On the basis of the work performed in our laboratory, the effects of various resuscitation fluids on cellular functions can be summarized as follows.

- Isotonic crystalloids: Significant immune activation and induction of cellular injury are seen with these fluids, especially LR. We know that a very large number of trauma patients receive LR and do well clinically. However, the patients that develop late complications of increased inflammatory response are usually the ones that also have undergone severe hemorrhagic shock and massive fluid resuscitation. Thus, LR may be safe in small doses that the body can obviously tolerate, but not in larger amounts given over short periods after hemorrhagic shock and trauma. Modifications of LR, such as substituting lactate for ketone bodies (or pyruvate) and elimination of D-lactate, hold promise.
- Hypertonic crystalloids: As compared with LR, hypertonic saline causes suppression of neutrophil oxidative burst activity and induces less cellular injury. Because of its logistic advantages and immunologic benefits, HTS with or without a colloid seems to be the ideal fluid today for military application. However, a manufacturer will have to obtain Food and Drug Administration approval for its use as a volume expander in the United States. Although addition of dextran to HTS tends to prolong the volume expansion response, we feel that it might be easier to obtain Food and Drug Administration approval for a simple solution (HTS) than for a combination solution (HTS and dextran).
- Artificial colloids: Dextran and Hespan cause the most pronounced neutrophil activation. However, combination of dextran with hypertonic saline blunts this response. When given in combination, they also prolong the hemodynamic response of hypertonic saline resuscitation.
- Plasma: This has the most favorable effect on neutrophil activation and numerous markers of cellular injury. Plasma is also a very effective volume expander. However, it has all the well-recognized problems that are associated with storage, transport, and infusion of blood products. Autologous freeze-dried plasma is a promising alternative that can be reconstituted in a hyperoncotic, hypertonic fashion when needed.
- Fresh whole blood: This is by far the best and most effective fluid for resuscitation of hemorrhagic shock. Fresh whole blood is, however, not clinically available. Even if available, the logistics of storage and transport make it an unrealistic option for the military. The military should implement the use of the walking blood bank whenever it is needed.
- Artificial blood: All the products tested to date have failed to live up to expectations. It is hoped that one day we will have an effective and safe oxygen-carrying artificial blood product.

RECOMMENDATIONS FOR THE INITIAL TREATMENT OF COMBAT CASUALTIES.

On the basis of our own research and review of contemporary data on combat casualty resuscitation, we propose a simple treatment algorithm (Fig. 8). Although this article deals primarily with resuscitation from hemorrhagic shock, for the sake of completeness we have added neurogenic shock to the treatment scheme. These recommendations are specifically for the initial field resuscitation; once the injured patient has been transported to a more stable environment, conventional methods may be used. The recommended algorithm has been based on the following information.

1. Most Combat Casualties Do Not Require Fluid Resuscitation

The vast majority of combat casualties are not in shock. Examining the casualty data from the last several military conflicts has shown that the vast majority of battlefield wounds are to the extremities and soft tissues as a result of firearms or fragments.[27] Most of these injuries can be treated initially without any fluid resuscitation. Whereas in civilian trauma practice the placement of an intravenous line is convenient, the same is not true for the initial care of an injured soldier. This can wait until the soldier has been removed from the line of fire and has arrived at the level of second-echelon care.

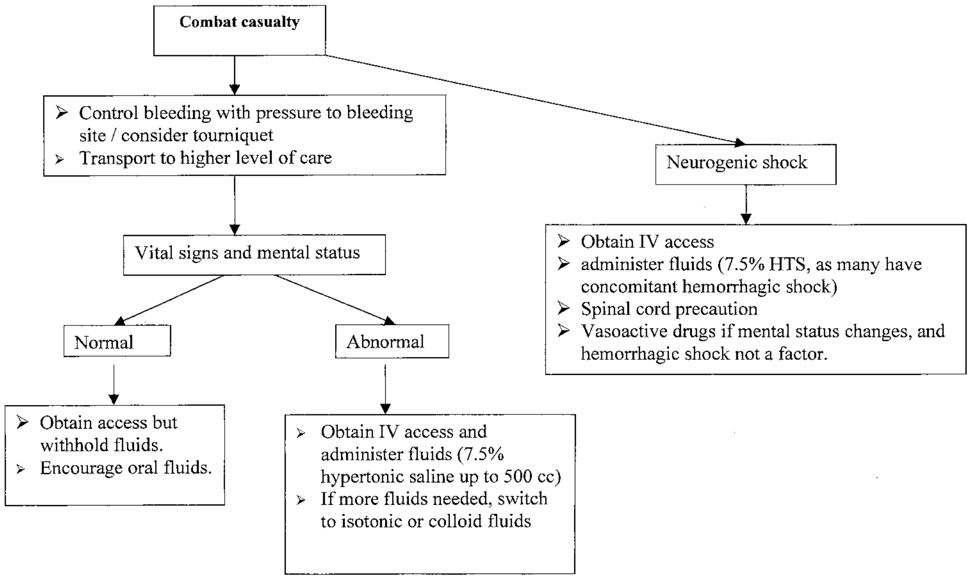

Fig. 8. *Algorithm for the initial resuscitation of combat casualties.*

2. Oral Hydration Is an Underused Option

In a civilian trauma setting, typically all oral intake is withheld during the early postinjury phase. This simplifies the evaluation process and decreases the chance for aspiration of gastric contents. This is a sound practice because most of the patients that need surgery are taken to the operating room rapidly. However, because of the changing environment in the military where transport to higher echelons of care may be delayed more than in previous battles, the use of oral hydration in soldiers that have injuries to the extremities makes sense. During the Korean War, typical transport times were approximately 4 hours. The Vietnam conflict saw that time reduced to approximately 30 minutes. The military conflicts in the future are expected to be similar to the battle in Somalia (1993),[27–30] where the delay in evacuation was several hours, and many of the casualties could not be evacuated until the next morning. The types of operations anticipated by the U.S. Marines will be over larger distances with a rapid nonlinear battlefront, as exemplified in the Desert Storm experience. The doctrine of the U.S. Marines engaging in operational maneuvers from the sea dictates that transport to casualty receiving facilities will be hampered by longer distances and priorities of rapid and violent engagements. Longer transport times, and the fact that the vast majority of wounded will not have life-threatening injuries, makes the oral route for hydration logical and convenient. Once out of the line of fire, obtaining vascular access in a stable environment is more appropriate. Currently, the natural instinct of providers is to start an intravenous line as soon as possible on all casualties and withhold oral intake. Although oral fluids are absorbed at a decreased rate in animal models of hemorrhagic shock, most of the injured soldiers are not in shock and do not need immediate intravenous fluid resuscitation. Finally, the possibility of aspirating gastric contents is a concern. In civilian trauma care, the chances of aspiration during induction of anesthesia are very low when rapid-sequence intubation is carried out. In fact, the vast majority of civilian trauma patients have a full stomach when urgent surgical care is provided. When the injured soldier finally receives surgical intervention under general anesthesia, it will be delivered at a higher echelon of care and in a controlled environment. Rapid sequence intubation in this setting can minimize the chances of aspiration.

3. Aggressive Resuscitation Has Not Been Shown to Be Beneficial in Civilian Victims of Penetrating Trauma

The test of this hypothesis in humans was published in the *New England Journal of Medicine* in 1994.[31] In this study, hypotensive patients with penetrating injury to the torso were randomized to routine fluid resuscitation, or the start of an intravenous infusion but no fluid resuscitation until surgical control of bleeding had been achieved. The rationale was that early fluid resuscitation would increase the blood pressure and thus make the patients bleed more from the uncontrolled source of hemorrhage. The results of the study demonstrated a survival advantage for the patients when initial crystalloid resuscitation was withheld. This study has generated vigorous debates and has been extensively scrutinized for its faults. One of the major criticisms had been that the study did not include the patients that died in the field in an "intent-to-treat" analysis. When all these were included in the analysis, it was discovered that withholding of fluids provided no survival benefit. The surprising aspect of this subsequent reanalysis remains the fact that the withholding of fluids showed no increase in mortality.

4. Moderate Resuscitation in Animal Models of Uncontrolled Hemorrhage Offers the Best Outcome

Some of the researchers have focused on the detrimental aspects of aggressive fluid resuscitation during the initial treatment of uncontrolled hemorrhage. It was speculated that the preservation systems of the body have a built-in set of compensatory mechanisms that would allow it to withstand moderate levels of shock. Animal models have actually demonstrated that aggressive resuscitation in the setting of uncontrolled hemorrhage could cause increased bleeding and thus worsen outcome. In this study, Burris et al.,[32] using a rat model of uncontrolled hemorrhagic shock via an aortic laceration, showed that the group that received no fluids had the lowest survival rate. The groups resuscitated with lactated Ringer's solution to a mean blood pressure of 100 mm Hg also had extremely low survival rates. The highest survival rates were seen in the animals that were resuscitated to a mean blood pressure of 80 mm Hg with LR, or 40 mm Hg with 7.5% hypertonic saline and 6% hetastarch solution.

5. Large Volumes of LR May Not Be Totally Innocuous

Since the inception of LR (Ringer, 1883), it has been widely used for the treatment of hemorrhagic shock, burns, and sepsis. However, its use has not been without controversy. Cushing recognized the cytotoxic effects of LR as early as 1901 in isolated nerve and muscle preparations. LR is a racemic mixture of two stereoisomers of lactate: D(−)-lactate and L(+)-lactate. The metabolism of these two lactates occurs via different pathways and produces distinct metabolic consequences. An increase in serum D-lactate alters neurologic function and produces encephalopathy.[33] D-Lactate has also been shown to produce various degrees of cardiac arrhythmogenicity, premature ventricular contractions, ventricular tachycardia, sinus bradycardia, ventricular fibrillation, third-degree heart block, and asystole.[34] We have recently reported that the two isomers of lactate exert markedly different effects on neutrophil oxidative burst and expression of a number key leukocyte regulatory genes.[14] With the recent advances in the capability to examine the immune response closely, there is accumulating evidence that the type of fluid used for resuscitation makes a difference. This article has summarized some of the data from our laboratory to substantiate this claim. We feel that it may be more prudent to develop and test a fluid that does not increase cellular damage rather than modulating the response after the process has already been set into motion.

6. Hypertonic Saline Administered Intravenously Has Been Shown to Be Safe in Dehydrated Animal Models of Hemorrhagic Shock

Numerous studies have tested the efficacy of hypertonic saline resuscitation in dehydrated animals subjected to hemorrhagic shock. Review of these data reveals that dehydration of up to 4 days (20% weight loss) does not compromise the efficacy of hypertonic resuscitation.[35] When compared with LR in a conscious, dehydrated (48 hours) swine model of hemorrhagic shock, 4 mL/kg of HTS with dextran (HSD) was found to be equally effective and safe.[36] Although dehydration increased the mortality (compared with the euhydrated group) from hemorrhagic shock, it did not affect the early hemodynamic response to HSD treatment.[37]

7. Hypertonic Saline Has Been Found to Be Safe in Eight Prospective, Randomized, Clinical Trails of Trauma Patients

The use of HTS for resuscitation from hemorrhage was first described in 1980, when Velesco et al.[38] and DeFelippe et al.[39] reported in separate studies that hyperosmotic sodium chloride rapidly expands plasma volume after major blood loss. These early studies generated a storm of experimental and clinical research examining the use of HTS for the early restoration of blood pressure and cardiac output in the field. Since then, HTS has been used in a variety of circumstances, and over 300 articles have appeared in the literature over the last 10 years. Recently, there have been eight double-blind, randomized trials evaluating HTS or HSD for prehospital or emergency department treatment of traumatic hypotension. Improved rates of survival after discharge were reported with HSD in seven of eight trials, although statistically significant improvement in overall survival was seen in only one trial. A meta-analysis for the evaluation of HSD as the initial treatment for hypovolemic shock reviewed the original records from six trials (and 604 subjects).[40] Overall discharge survival rates were better with HSD resuscitation as compared with conventional resuscitation. HSD resuscitation seems to be particularly effective for the subgroup of patients that have sustained head injury, with a discharge survival rate of 38% compared with a rate of 27% for the control group receiving saline. In the clinical literature, there has been a remarkable absence of deleterious effects with HTS administration in more than 1,000 trauma and surgical patients. No increase in the incidence of hypernatremic seizure, increased bleeding or blood transfusion requirement, coagulopathies, renal failure, cardiac arrhythmias, or central pontine myelinolysis has been attributed to hypertonic resuscitation in trauma patients.

8. IOM Has Recommended 250 mL of 7.5% HTS Infusion for Initial Use in Resuscitating Combat Casualties and a Second Bolus of 250 mL If Necessary

As previously mentioned, the Institute of Medicine report has made a recommendation to use 7.5% HTS (up to 500 mL) for the treatment of battlefield casualties in shock.[5] Although HSD may have theoretical advantages over HTS, the report by the IOM states that there is no convincing evidence that HTD has any major advantage over HTS in the early treatment of hemorrhagic shock.

9. HTS Offers Significant Advantage in Terms of Weight and Cube for the Military Medic or Corpsman

Carrying fluids in the field is difficult because of their weight (1 L of fluid weighs 1 kg). However, the use of 7.5% HTS can provide the same hemodynamic response as isotonic fluids with only one eighth to one tenth the volume (and weight). Even though the clear superiority of HTS is debatable, there is no evidence that HTS used as the initial resuscitation fluid is worse than isotonic solutions. Our recommendation is not to use this fluid as the only resuscitation fluid. Because hypertonic saline may not be the best fluid to use over long periods of time, a combination of hypertonic saline and LR should be available in the field hospitals. However, use of hypertonic saline as the first fluid in the far-forward area would markedly improve the logistics involved.

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